specification allegedly fails to enable the full scope of subject matter encompassed by the claims. Specifically, the Examiner contends that both the device and method claims of the invention require exhaustive support in the form of in vivo, therapeutic examples, which the Examiner asserts are lacking in the specification. In this context, the Examiner has reviewed Applicants' submissions of in vivo examples in the specification and elsewhere, including in vivo examples teaching detailed uses of the invention in rats, dogs and non-human primates, and has deemed these submissions unconvincing of enablement for any of the claims under consideration.

Applicants respectfully traverse the stated grounds of rejection under 35 U.S.C. § 112 and submit that their disclosure enables the full scope of the claimed invention.

i) The Enablement Standards Applied to Applicants' Disclosure Exceeds the Proper Scope of Enablement Analysis Required Under 35 U.S.C. § 112

The Examiner's objections to the specification impose overly restrictive and unduly burdensome standards of review, which exceed the proper scope of review and substantive enablement requirements under 35 U.S.C. § 112. Specifically, the Examiner calls for in vivo working examples for all claims, which examples are required to fulfill a strict "therapeutic paradigm" characterized by: (1) achieving a therapeutic use in all animals including humans, and in all patients within each animal group; (2) providing efficacious therapy using all genes disclosed by Applicants to be "of interest"; and (3) fulfilling a rigorous model of gene therapeutic efficacy requiring "long term", "precisely regulated expression" (emphasis added).

The requirements set forth in the Office action as applied to Applicants' disclosure contravenes the patent statutes and governing case law, and is believed to be inconsistent with

the PTO's own administrative rules and guidelines. According to the Examiner, none of Applicants' devices or methods can be enabled without exhaustive in vivo therapeutic examples, which the Examiner concludes are not to be found among the numerous working examples provided by Applicants. To support this conclusion, the Examiner poses an insoluble standard of in vivo efficacy by requiring that, if any of Applicants' claims can be read within a "therapeutic paradigm," Applicants must enable even the most far-reaching and unpredictable uses throughout this ostensibly limitless paradigm. Even for Applicants' straightforward engrafting device claims, the Examiner calls for proof that the device will work in every gene therapeutic application (i.e. for all genes, all vectors, and under the tightest and most complex regulatory schemes and long term expression regimens conceivable), and will be therapeutic in all cases (i.e. for all patients among all animal groups).

This is clearly an improper foundation for asserting non-enablement of Applicants' claims, particularly with regard to claims directed to engrafting devices and the corresponding in vivo methods. Contrary to the Examiner's imposed standards, Applicants note that there is only required to be a "reasonable correlation" between their disclosure and the scope of protection sought in their claims. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 706.03(n). In this context, Applicants' amended claims recite engrafting devices "for implanting autologous vascular smooth muscle cells transduced with a gene of interest into a mammalian subject," and methods "for introducing a gene of interest into a mammalian subject," or "delivering a therapeutic product to a mammalian subject." It is intended that these claims read on similarly structured devices, as well as in vivo methods which employ the devices.

Each of these basic embodiments of the invention are supported by detailed, in vivo examples, including in vivo

examples teaching successful use of Applicants' devices and methods for experimental, diagnostic, prosthetic and gene therapeutic uses in rats, dogs and non-human primates. The examples and supplemental data provided in the record clearly establish that the disclosure of Applicants' invention corresponds "reasonably" to the scope of the claims. Indeed, the scope of enablement provided fulfills even the most stringent requirement for enablement of in vivo methods and uses.

ii) The Substantive Enablement Criteria Set Forth By the Examiner Are Also Improper

Aside from applying an unduly burdensome scope of enablement review, the Examiner has imposed discrete enablement criteria and findings against Applicants' disclosure which also fail to comport with standards set forth under 35 U.S.C. § 112.

In one important example, the Examiner characterizes the entire field of gene therapy as suffering from an "exceedingly high level of unpredictability." However, the Examiner makes no attempt to tailor or support this finding in the context of Applicants' distinct technology and teachings, or to reconcile this blanket conclusion with Applicants' detailed rebuttal evidence submitted in the record.

To clarify these issues, Applicants refer to Example G "Gene Therapy" presented in the Training Materials for Examining Patent Applications With Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications (hereinafter "Enablement Guidelines"). In this example, a hypothetical disclosure describes viral vectors for delivering genes of interest into mammalian cells. Sample vectors incorporating various genes of interest are provided and shown to infect cells and cause them to produce corresponding proteins of interest in vitro. Notably, as emphasized in the Guidelines, "[t]he specification [of the hypothetical disclosure] does not

show any examples relating to gene therapy or any in vivo use of the viral vectors."

According to the Guidelines under this type of scenario, a non-environmentally or methodologically limited claim to the viral vector is considered allowable, on the basis that, "because it does not recite any environment of use, only one enabled use covering the scope of the claim is needed to enable the claim." For analogous reasons, Applicants' device claims 1-10 should clearly be allowable, as discussed in further detail below.

Other claims in the hypothetical of Example G are deemed non-enabled in the recitation of "therapeutically effective" compositions, or in vivo methods covering gene therapy. The primary basis for this non-enablement determination is that the hypothetical disclosure "fails to provide any guidance regarding gene therapy, such as dosages, routes of administration, and working examples." Indeed, as noted above, the hypothetical disclosure lacks any examples of in vivo use of the claimed vectors. In addition, the Example states that the state of the art, with respect to the use of vector compositions for gene therapy, is "highly unpredictable and undeveloped."

These substantive findings pertaining to Example G contrast sharply with the teachings and examples of Applicants' disclosure. Most importantly, Applicants' disclosure provides detailed in vivo examples using a variety of claimed embodiments of the invention in a range of model systems. These examples enable a broad scope of in vivo uses for Applicants' invention, over and above the degree of guidance and predictability afforded by the limited, in vitro examples described in Example G.

With regard to the "route of administration" addressed in Example G, Applicants' note that both the mode and route of delivery of their claimed methods are pre-defined by in vitro

transduction and local engrafting of smooth muscle cells. This modality and route of delivery adds a great deal of reliability and predictability over systemic vector delivery, the latter of which exposes vectors to inactivation by serum factors prior to their infection into target cells. This primary weakness of in vivo transduction gene therapy (featuring poorly defined, in vivo targeted cell populations, wherein vector delivery, targeting, infection success and inactivation are relatively unpredictable) should not be imputed to Applicants' methods, which clearly avoid these difficulties and have in fact been demonstrated to be broadly successful in vivo.

With regard to the state of the art and level of skill pertaining to Applicant's disclosure, the Examiner generally asserts a lack of predictability in using different vector systems for in vivo gene transfer, pointing specifically to the demands of tissue specific vector constructs, and the possibility of vector inactivation in vivo. The Examiner specifically contends that even the routine technology of cellular transduction is inherently "unpredictable," quoting an anecdotal statement from the Jolly article that retroviral vector construction is a "mixture of art and science". This statement is proffered by the Examiner as "evidence" of a low level of skill and predictability in the art. However, this conclusion ignores the important fact that the quoted remark was directed toward constructs using complex, tissue specific promoters, which cannot be compared for enablement purposes to Applicants' constructs, proven by Applicants to be useful within a claimed environment drawn to smooth muscle cell type[1].

---

[1] Far from establishing a low level of skill and predictability in the art, the cited article by Jolly actually teaches that a reasonable percentage of "one in five" retroviral constructs using tissue specific promoters "will behave satisfactorily."

In summary, the Examiner has provided no evidence that the use of different vector systems to transduce smooth muscle cells to express different genes of interest within Applicants' invention would require undue experimentation. As previously noted, Applicants' invention does not rely on the particular vectors and genes chosen to implement the invention, but in the proven devices and methods for engrafting transduced vascular smooth muscle cells into a mammalian subject to deliver useful proteins. Choice of vectors and genes to achieve successful adaptation of these devices and methods, based on Applicants' teachings and general knowledge in the art at the time of the invention, would require no more than routine manipulation and optimization of known parameters.

Clearly, a wide variety of suitable vectors for use within the invention are disclosed in the specification and were generally known in the art. For use within the invention, a variety of vectors are clearly suitable and routinely adaptable for expressing a diverse assemblage of genes in transduced vascular smooth muscle cells. As noted in the Specification, these vectors will generally be retroviral vectors. As also documented in the specification and elsewhere in the record, these vectors can be routinely used to transduce vascular smooth muscle cells to provide a defined population of cells containing stable integrants, that express a selected gene for a substantial period of time as demonstrated by the evidence of record.

In addition to the routine adaptability and predictability of operable vectors for use within the invention, it is also clear that the vast majority of cDNA's corresponding to "genes of interest" (i.e. expressing useful proteins for <u>in vivo</u> experimental, diagnostic and/or therapeutic purposes) can be accommodated in retroviral vectors, including, e.g., the cystic fibrosis transmembrane conductance regulator at about 4 kb. Even larger genes, e.g., greater than 8 kb, can be accommodated in

other vectors, e.g., the foamy virus group of retroviruses, as is described in the literature.

As an additional note, the Examiner formerly cited Anderson (Human Gene Ther.) for the proposition that many viral promoters are shut off in primary cells in vivo. However, it is clear that this problem is also improperly imputed to Applicants' disclosure. As previously indicated, smooth muscle cells have not been demonstrated to inactivate retroviral expression sequences. On the contrary, as noted, for example, at page 11 of the Lejnieks et al. manuscript (Exhibit 4 to Applicants' April 2, 1996 Amendment):

> Our data show that transduced vascular smooth muscle cells do not inactivate retroviral vector sequences, in agreement with previous studies of retrovirally-mediated gene expression in these target cells (Lynch et al., 1992; Clowes et al., 1994; Osborne et al., 1995). This is in contrast to skin fibroblasts where vector inactivation has been documented in both rats (Palmer et al. 1991) and dogs (Ramesh et al., 1993). Thus, data is accumulating to show that vascular smooth muscle cells provide an ideal target tissue for gene therapy.

With regard to Applicants' working examples in the specification, the Examiner asserts that successful transduction and expression of the enzyme, lac Z, and the product of the PNP gene, would not be accepted as evidence that the invention can achieve in vivo delivery of a therapeutic product with a reasonable expectation of success. Applicants emphatically disagree. Lac Z (encoding an ordinary enzyme β-galactosidase, which itself can be used as an exogenously delivered therapeutic product to treat galactosidase deficiency in humans) is widely employed and accepted as a model for expressing other useful proteins in vivo, for research, diagnostic as well as therapeutic purposes. As documented in Applicants' specification, Lac Z was

successfully expressed in non-human primates in vivo in a sustained protocol to locate, identify and enumerate transduced cells in prosthetic grafts, before and after engraftment.

Applicants' work with the Lac Z gene as a model for gene therapy expression was accepted and published in peer-reviewed scientific journals. See, for example, Geary et al., Human Gene Ther. 5: 1211-1216 (1994), provided as Exhibit 3 to Applicants' April 2, 1996 Amendment. However, the Examiner has assumed the position that "publication of research is not grounds for satisfying the requirements of enablement." Applicants believe that the Examiner's interpretation is inconsistent with 35 U.S.C. § 112, and with the rules and cases implementing and interpreting this statute. Specifically, Applicants contend that publication of their device and methods in widely disseminated, peer reviewed articles serves as prima facie evidence, not only of the "credibility" of Applicants' methods and results, but also of the consistency of Applicants' methods and results with accepted methodology and scientific reasoning and opinion. The fact that Applicants' use of the Lac Z gene has been embraced and incorporated into the literature for in vivo delivery of protein products using Applicants' novel engraftment devices, clearly provides further probative evidence of enablement regarding the claims presented for review. In particular, peer review and publication of Applicants' methods and results evinces comprehension and acceptance of Applicants' teachings among ordinarily skilled artisans, and further suggests that Applicants' working examples are accepted in the art as valid models and embodiments of in vivo delivery of protein products.

With regard to the use of animal models, the Examiner cites Ledley for the proposition that animal experiments may be poorly predictive of gene therapy results in humans. As Applicants previously noted, this conclusion is certainly inconsistent with the Anderson Declaration (Exhibit 1 to

Applicants' April 2, 1996 Amendment), which established that, by October 1993, 38 human clinical trials had been approved by the FDA and the RAC of the NIH, each approval undoubtedly based in part on accepted animal model results. The animal models employed by Applicants are in fact widely accepted by artisans in the field, as further evinced by acceptance of Applicants' work in peer-reviewed scientific publications. Thus, the working examples described in the Specification, as well as later work by Applicants using other models, clearly support the teachings of Applicants' Specification.

It is also noteworthy in this regard that the Ledley citation specifically attributes unpredictability of animal models to a variety of factors, including the predictability of "outcome, efficacy, or safety of human applications." These factors are largely overcome by Applicants' in vitro transduction/engrafting methods, in contrast to conventional gene therapy involving in vivo vector delivery (see below). The Ledley article also mentions the possibility of "species specific" infectivity, tropism and pathology of retroviral vectors, which the Examiner alleges to evince "species differences in the efficiency of tissue culture, transduction and expression of human smooth muscle cells, compared to results presented in the animal model." Applicants submit that the cited reference fails to support the Examiner's conclusions, and that no evidence has been provided in the record to support the alleged species differences in smooth muscle cell culture, transduction and expression. On the contrary, the Examiner is respectfully directed to Applicants' examples and data of record establishing successful smooth muscle cell transduction among different species, and to Lejnieks, ibid, at page 11, where it is stated that:

> [V]ascular smooth muscle cells provide an ideal target tissue for gene therapy. These cells are

> readily obtained, cultured, transduced and returned to their donor. Implantation of these cells in the blood circulation suggests their use for the secretion of not only hormones but also clotting factors for the treatment of patients with hemophilia and enzymes for treatment of lysosomal storage disorders.

If the Examiner is aware of any evidence contrary to these findings and conclusions, which evidence provides a factual showing that adaptation of smooth muscle cell transduction between humans and other mammals would require undue experimentation, Applicants request that it be made of record for Applicants' review and opportunity for rebuttal.

To further address the Examiner's argument that gene therapy suffers an "exceedingly high level of unpredictability," Applicants again refer to the Declaration by Anderson on record in U.S. Patent No. 5,399,346 (issued to Anderson et al.; previously submitted as Exhibit 1 to Applicants April 2, 1996 Amendment) which summarizes the general predictability of gene therapy, as follows:

> "2. He [Anderson] has attached hereto as Exhibit 1 a list of human gene therapy protocols, and to the best of his information and belief, the protocols listed as 1-38 have been approved by the Recombinant DNA Advisory Committee (RAC), a committee of the National Institutes of Health....
>
> ***
>
> 4. The approved protocols 5-38 are directed to human gene therapy with a variety of DNA sequences, employing a variety of delivery vehicles, and are directed to both ex vivo and in situ (in vivo) transduction of human cells. Thus, for example, such protocols include the following:
>
> 1. TNF, which is a secreted cytokine
> 2. IL-2, a secreted lymphokine;
> 3. LDL receptor, a membrane protein;
> 4. TK, an activatable viral gene;
> 5. HLA-B7, a cell surface antigen;

6. HIV-gp120, a surface antigen;
7. IL-4, a cytokine;
8. antisense-RAS, an antisense molecule to an oncogene;
9. p53, a tumor suppressor gene;
10. CF, an integral membrane transport protein;
11. GM-CSF, a hematopoietic colony stimulating factor;
12. gamma interferon, a cytokine;
13. MDR, a membrane transport protein;
14. glucocerebrosidase, an intracellular enzyme;
15. mutated HIV, a viral protein;
16. Rev, a viral transcription factor;
17. anti-IGF-1, an antisense molecule to a cell growth factor; and
18. ribozyme, an RNA-cleaving RNA molecule.

> In addition, the RAC-approved protocols encompass a wide variety of delivery means, such as retroviral vectors, adenovirus vectors, liposomes for delivery of plasmid DNA, and viral-producer cells....
>
> ***
>
> 5. To the best of his information and belief, the RAC does not approve a human gene therapy protocol unless there is a reasonable expectation of efficacy....[I]t was now possible for those skilled in the art to design and obtain RAC approval for a wide variety of human gene therapy protocols. [Declaration of W. French Anderson, M.D., dated October 15, 1993, in file of US Pat. No. 5,399,346; emphasis added.]

As the Anderson Declaration documents, examples of each different type of gene product alleged by the Examiner to contribute to non-enablement of the invention (enzymes, cytokines, receptors, hormones, growth factors, and coagulation factors) have been accepted for clinical trials for human gene therapy.

As previously emphasized by Applicants, "the RAC does not approve a human gene therapy protocol unless there is a reasonable expectation of efficacy." Even though the Examiner does not disagree with this statement, the predicted efficacy of gene therapy correlated with RAC approval is nonetheless

dismissed by the Examiner as not having any "specific bearing" on enablement of the invention. Applicants note that the Anderson declaration is as relevant or irrelevant to enablement of Applicant's invention as the articles relied on by the Examiner, which in fact do not address the claimed invention. Applicants also strongly disagree with the Examiner's position regarding RAC approval evidence, and submit that RAC and FDA approval each provide prima facie evidence that the methods and results on which such approval is based comport with accepted scientific methodology and opinion. The fact that gene therapy spanning the various methods and components embraced within the Anderson Declaration has been developed and accepted to the point of widespread adoption within human clinical trials, clearly evinces a state of the art and level of skill for practicing gene therapy that is probative and supportive of enablement for Applicants' invention. Accordingly, the Examiner's dismissal of this evidence as having no specific bearing on this question is believed to be in error.

In specific regard to "dosages" and "working examples," Applicant's disclosure and supplemental evidence of record also contrasts favorably with the hypothetical disclosure of gene therapy Example G provided in the Enablement Guidelines. Specifically, Applicants have described extensive and detailed in vivo uses of their devices and methods, including successful adaptation of the invention to rat, dog and non-human primate in vivo systems. Among these examples, Applicants proffered evidence establishing in vivo expression of therapeutic levels of granulocyte-colony stimulating factor (G-CSF) manifesting sustained, therapeutic increases in neutrophil levels in rats and dogs using Applicants' engrafting devices and methods (as offered or submitted previously in the record, for example, in Applicants' April 2, 1996 amendment and supporting exhibits). Likewise, Applicants demonstrated long-term, therapeutic levels

of erythropoietin (EPO) expression manifested by therapeutic increases in hematocrit levels in rats using their engrafting devices and methods, and provided supporting models in dogs and baboons which exemplify adjustable delivery of EPO at different levels based on seeded cell number and graft size. (id.). All of these results follow the teachings and working examples of Applicants' specification, whereby the scope of Applicants' disclosure clearly corresponds to the full scope of the present claims.

Despite the foregoing evidence regarding the breadth and substance of Applicants' disclosure, the Examiner posits a strict determination that Applicants have failed to enable any in vivo uses for their engrafting devices and methods. In this regard, the Examiner makes no distinction between gene therapy examples that rely on in situ, or in vivo, delivery of vectors, and Applicants' far more controlled and predictable, in vitro transduction/engrafting devices and methods. This distinction is clearly relevant to the present enablement analysis, because Applicants' methods and devices deliver a pre-transduced, defined cell population, engrafted to a pre-determined site accessible to the circulation, in a pre-determinable number, which engrafted cells have been proven to yield prolonged expression of selected therapeutic products. At the same time, Applicants' devices and methods for delivering therapeutic products are relatively free of vector inactivation problems that attend in vivo vector delivery. Further, Applicants' seeding of transduced cells within implants greatly diminishes any potential hazards of translocation of harmful cells from the site of delivery, and the removability of Applicants' grafts further minimizes attendant risks of conventional gene delivery methods.

The Examiner takes no specific notice of any of these facts that distinguish Applicants' devices and methods for enablement review purposes. Instead, the Examiner imposes a

blanket objection to Applicants' specification, which objection contradicts the evidence of record documenting extensive and detailed in vivo uses of Applicants' devices and methods, as discussed above. Moreover, the Examiner's reasoning is subject to criticism for requiring the disclosure to conform to a strict "therapeutic paradigm" characterized by achieving therapeutic use in all subjects with all genes on a "long-term," and "precisely regulated" basis.

It is clearly not Applicants' burden to prove their invention useful for all vectors and genes, for all modes and levels of gene regulation, and to achieve therapeutic effects in all patients. For Applicants' therapeutic method claims, enablement only requires that the specification teach in vivo use of their device sufficient to achieve therapeutic protein delivery in a mammalian subject without undue experimentation.

Contrary to the Examiner's proffered evidence and arguments, enablement of the instant claims does not require examples of "precisely regulated" and "long term" gene expression. It is sufficient to achieve therapeutic protein expression commensurate with the scope of Applicants' claims by delivering even a basal level of a therapeutic product, and even on a relatively short term basis. Applicants believe that this assertion holds true for EPO and G-CSF, as well as for other exemplary therapeutic products within the invention, including insulin, which the Examiner asserts must be tightly regulated to confer any therapeutic value.

In contrast to the Examiner's position, gene therapy involving "[u]nregulated low level insulin gene expression from the liver" (notably by in vivo administration of a retroviral vector), has been proven efficacious in controlling severe diabetes in rats, as evinced by insulin and glucagon levels, blood ketones and other catabolic activity indicators. Kolodka

et al., *Proc. Natl. Acad. Sci. USA* 92: 3293-3297, 1995, copy enclosed for consideration).

In other studies, low, "prophylactic" levels of insulin have been demonstrated to delay or prevent the onset of insulin-dependent diabetes mellitus (IDDM) in BB rats and nonobese diabetic (NOD) mice, two widely accepted models of spontaneous IDDM in humans (Schloot et al., *Immunology Today* 16: 289294, 1995; Gotfredsen et al., Diabetologia 28: 933-935, 1985; Kaufman et al., Nature: 366: 69-71, 1993, copies enclosed for consideration), as well as in humans (Robertson et al., Diabetologia, 35 [Suppl 2]: S8-S17, 1992, copy enclosed for consideration). As explained in Gotfredsen et al., it is probable that exogenous insulin administration is therapeutically effective even at the low prophylactic levels tested, because it reduces endogenous insulin secretion that would otherwise elevate autoimmune activity against B-cells.

Accordingly, it is submitted that insulin delivery employing the methods and devices of the invention can be achieved at the same prophylactic levels shown to be therapeutic in the above studies, without undue experimentation. In this context, insulin levels sufficient to have a therapeutic effect would be evident to the clinician monitoring such a patient, and are routinely monitored in diabetic patients.

In yet additional studies bearing on enablement of the invention, low level, prophylactic delivery of Factor IX by in vivo gene therapy in dogs resulted in therapeutic decreases in whole blood clotting and partial thromboplastin times of the treated animals (Kay et al., *Science* 262: 117-119, 1993) was enclosed for consideration. This study, which also involved a comparatively unpredictable, in vivo retroviral gene transfer compared to Applicants' in vitro transduction/engraftment technology, supported the conclusion that:

> Our study demonstrates the feasibility of in vivo retroviral-mediated gene transfer into the liver of a large animal, which results in phenotypic improvement of a deficiency syndrome. The factor IX antigen amounts achieved after gene transfer were only about 0.1% of the endogenous concentration of factor IX in normal animals, which demonstrates that the constitutive expression of a relatively small quantity of the factor IX protein is sufficient to cause a reduction in the WBCT and a shortening of the PTT. (id., at page 119)

Commenting further on these studies, and specifically extolling the benefits of low level constitutive expression of gene therapeutic products, a contemporary review of the Kay et al. study (Marx, *Science* 262:, 29-30, 1993) concluded that:

> [E]ven though the animals aren't making very much of the (factor IX) protein, even that small amount has significantly reduced their blood clotting times; from 50 minutes before treatment to about 20 minutes . . . .. (Human) patients who make as little as 1.5% of the normal amount of clotting factor do much better than the majority of hemophiliacs, who make less than 1%.

In addition to the insulin example, the Examiner also asserts that it is necessary to tightly regulate erythropoietin (EPO) expression to achieve any therapeutic value from its delivery via the methods and devices of the invention. To the contrary, Applicants submit that it is also not necessary to tightly regulate EPO for therapeutic use within the invention. As in the case of insulin and factor IX delivery, low, constitutive levels of exogenous EPO would be expected to confer significant therapeutic benefits to anemic patients, which benefits could be achieved by the ordinarily skilled artisan practicing the Applicants' teachings with only routine manipulation and optimization of parameters.

As shown in Exhibit 2 to Applicants April 2, 1996 Amendment (Osborne et al., Proc. Natl. Acad. Sci. USA 92: 8055-8058, Aug. 1995), an article that includes co-inventors as co-authors, long-term therapeutic expression of EPO in rats has been achieved using transduced vascular smooth muscle cells for greater than seven weeks, and subsequent data have been obtained for expression out to greater than nine months. As noted therein:

> These data indicate a relatively efficient seeding procedure that results in a cell mass capable of providing sustained gene delivery at therapeutically significant levels. [p. 8057; col. 1, first para; emphasis added.]
>
> ***
>
> The constitutive level of Epo we achieved in this study would provide useful therapy for patients with renal failure. Although arterial seeding is not feasible in human subjects, we have recently shown in baboons that prosthetic vascular grafts can be used as a device to implant transduced cells. From the data produced in this rat model and our studies in dogs and baboons, we estimate that 10^8 transduced vascular smooth muscle cells can provide a therapeutic dose of Epo to an 80-kg patient, and this cell number could be transplanted in a 10 cm x 4 mm prosthetic graft.... The ability to treat these patients, and others with Epo-responsive anemias, by gene therapy would provide major clinical and economic benefits. [p. 8057, col. 2, lines 13-30; citations omitted; emphasis added.]

It should be further noted in this context that Applicants can modulate delivery of EPO and other therapeutic products within the invention to achieve therapeutic levels of delivery, unrealized by other modes and routes of gene therapy. In fact, Applicants are able to pre-determine the amount of erythropoietin that is secreted per cm. of graft containing transduced cells. Thus, Applicants can adjust delivery of EPO to

achieve a desired hematocrit by altering the length of grafts or density of seeded cells (see, e.g., McCarthy, Exhibit 5 to Applicants April 2, 1996 Amendment).

In view of the foregoing, the Examiner's skepticism regarding in vivo delivery of insulin, EPO and other therapeutic products using the methods and devices of the invention is not borne out by in vivo examples provided by or on behalf of Applicants, and elsewhere known and routinely practiced in the art. If the Examiner has a basis for believing otherwise, this information should be provided so Applicants can properly address it.

ii) The Rejection of Applicants' Basic Device and Method Claims Under 35 U.S.C. § 112 Lacks Proper Foundation, Because the Scope of These Claims Was Erroneously Construed

Applicants' basic device and method claims may have been erroneously construed by the Examiner to require the same type and level of support as claims drawn to specific therapeutic methods. Applicants submit that further evidence is unnecessary to prove the enablement of their basic engrafting device and method claims. The examples in the specification teach successful implantation of Applicants' engrafting devices in a variety of in vivo systems, and these examples are "reasonably correlated" with the full breadth that the Examiner should have attributed to these claims for enablement review purposes.

While it is the Examiner's duty to "clarify" the intended scope of the claims, the goal of this practice is solely "to provide the public with notice as to the patentee's scope of protection." (quoting from the Enablement Guidelines, at Section III(A)(1)). In this context, Applicants submit that it was improper for the Examiner to interpose environment of use and methodological paradigms to expansively construe their device and non-therapeutic method claims. These claims do not require the

stringent support advocated by the Examiner, i.e., in vivo examples in all animals including humans, coupled with proof of "long term", "precisely regulated expression" of all contemplated genes to achieve therapeutic effects in "all patients."

On the contrary, to require this type and level of support for any of the pending claims, particularly the device claims, transforms the first step of the enablement analysis, claim construction, into a self-fulfilling exercise of claim abstraction to reach a hypothetical extreme. Such an approach overlooks the purpose and mandate of the statute to literally construe the claims to provide reasonable notice to the public concerning their scope.

It is a well established rule of law that :

> A patent applicant is not required ... to predict every possible variation, improvement or commercial embodiment of his invention." Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1074 (D.Del. 1987).

In fact, all that 35 U.S.C. § 112 requires is that there be a "reasonable correlation" between Applicant's disclosure and the scope of the claims, having due regard for the nature of the invention and the state of the art. (See, e.g., In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); Ex parte Jackson, 217 USPQ 804, 807 (Bd.Pat.App.Int. 1982); In re Fisher, 166 USPQ 18, 24 (CCPA 1970); MPEP § 706.03(n)). The law expressly does not require a specification to function as a "blueprint," setting forth every operable and inoperable species encompassed within the claims. Staehelin v. Secher, 24 USPQ2d 1513, 1516 (Bd.Pat.App.Int., 1992). As explained by the Federal Circuit's predecessor court in In re Angstadt, 190 USPQ 214, 218 (CCPA 1976):

> [S]uch a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual

> experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ....

Based on these considerations, the Angstadt panel held that a patent applicant is "*not* required to disclose *every* species encompassed by their claims even in an unpredictable art." (id) (emphasis in original). The disclosure requirement of 35 U.S.C. § 112 therefore calls for only a representative range of species to be enabled within the claims, i.e., an assemblage of enabled species that is "reasonably correlated" with the full scope of the claims. Moreover, this representative assemblage need not be disclosed directly in the specification, or proven operable by working examples. On the contrary, so long as it does not require undue experimentation to obtain these representative species and demonstrate their operability, then the disclosure is sufficient.

This is a profoundly distinct standard from that advocated by the Office, which would require that Applicant's teachings enable use of the device for all genes of interest and all vectors, to achieve therapeutic results in all patients. This requirement for comprehensive production and testing of every possible species within the invention was expressly criticized by the court in Angstadt, supra, which emphasized that such exhaustive testing would often be "prohibitive," and "would tend to discourage inventors from filing patent applications in an unpredictable area."

If comprehensive production and testing is prohibitive for inventors in unpredictable arts, then it cannot be expected

by the Office that such comprehensive testing should be enabled to be routinely undertaken by other persons of ordinary skill in the art. On the contrary, the purpose of 35 U.S.C. § 112 is to ensure that the essential aspects of the invention are rendered available to the public, and that competitors can reasonably determine whether subject matter falls within the scope of the claims. The statute does not require that all species comprehended within an invention must be conveyed to one's competitors. Rather, those competitors need only be provided with sufficient information to determine whether a particular species of interest falls within the scope of the claims.

To require otherwise would directly contravene the holding and policies set forth in Angstadt. In unpredictable arts, or in circumstances where claimed genera embrace large numbers of species, the mandate for comprehensive enablement would become a self-defeating prophecy. Applying such a standard to limit an applicant's claims clearly would invite competitors to avoid literal infringement by finding one undisclosed species. The more appropriate standard is to ask whether that competitor can reasonably determine if any one species of interest falls within the scope of the claims.

Decisional law makes it quite clear that enabling all species within a claim is not required. Contrary to the Office's assertion, Applicants only need to enable a "reasonable" number of species; i.e., a representative sample "commensurate" with the scope of the claims. To achieve this "commensurate" assemblage of species, "a considerable amount of experimentation is permissible." Ex parte Jackson, 217 USPQ 804, 807 (Bd. Pat. App. Int. 1982).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. (id.) (emphasis added)

Reasonable experimentation to use Applicants' devices and methods can equal the same scope and complexity of experimentation that is ordinarily considered practicable and reasonable in the art, even if such experimentation is extensive and the art is unpredictable. Considering the guidance provided in the specification and the level of skill in the art, "reasonable experimentation" encompasses those methods and procedures that do not require "ingenuity beyond that to be expected of one of ordinary skill." (See, e.g. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984); In re Angstadt, supra. As the Angstadt panel emphasized:

> Appellants have broadly disclosed a class of catalyst complexes whose use they deem to be part of their invention. But for this disclosure the public may have been deprived of the knowledge of appellants' process. In this art the performance of trial runs using different catalysts is "reasonable," even if the end result is uncertain, and we see no reason on this record why appellants should not be able to claim as their invention the broad range of processes which they have discovered. (id., at 219) (emphasis added).

Applicants submit that the level of skill in the present arts is high. Thus, the ordinarily skilled artisan is equipped with extensive tools and training with which to implement and adapt Applicant's teachings to produce and select of operable species within the invention. Further, Applicants' teachings provide detailed directions and guidance for those skilled workers, which include clear instructions of how to make and determine operability of the invention. The Office has proffered no evidence to show that it would be unreasonable, or would require ingenuity beyond that of the ordinarily skilled artisan, to obtain a representative assemblage of operable species commensurate with the scope of Applicant's claims.

To support a reasonable scope for their basic device and method claims, Applicants demonstrated that autologous transduced smooth muscle cells, immobilized on pores and surfaces of their vessel grafts, exhibited prolonged survival and expression of various genes of interest in numerous, detailed in vivo examples. A primary method and use for Applicants' device, as a simple prosthetic vessel graft (see, eg. claims 16-17, and pp. 16-19 of specification), was clearly exemplified by data showing the graft surface to be anti-thrombogenic, promoting long term survival and patency of the engraftment devices in vivo in a variety of hosts, including non-human primates. Thus, Applicants have clearly fulfilled the enablement requirement for their device claims, simply by teaching how to prepare and successfully implant their grafts seeded with autologous, transduced smooth muscle cells. As set forth in the Enablement Guidelines, at Section III(A)(1), Applicants note that:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of section 112 is satisfied [case citations omitted].

As Applicants have addressed in more detail elsewhere herein, their basic devices and methods are fully enabled for gene therapeutic applications in mammals, including humans. However, it is unquestionable based on the more fundamental teachings discussed herein and elsewhere in the record that these devices and methods are also immediately available and useful for a diverse array of less detailed therapeutic, diagnostic and research oriented uses, some of which contribute directly to confirming the enablement of more specific uses contemplated within the invention.

For example, in addition to providing improved vascular prostheses, Applicants also teach how to make and use their engrafting devices for a range of related in vivo uses. In one such related use, the specification and other data of record exemplify in vivo gene expression by transduced smooth muscle cells within Applicants' engrafting devices, which expression is demonstrated to be operable and sustainable in a variety of hosts, including non-human primates. By describing additional grafts seeded with autologous cells transduced to stably and reproducibly express antithrombogenic proteins (eg. plasminogen activator or antithrombin III), Applicants have clearly provided powerful research and therapeutic tools, for example to study, diagnose and treat restenosis following vascular grafting or balloon angioplasty.

In this context, restenosis must be recognized by the Examiner to be particularly amenable to treatment using Applicants' devices and methods. As was generally known at the time of Applicants' invention, restenosis is an acute phenomenon following vascular injury or grafting procedures, which phenomenon involves thrombogenesis accompanied by aberrant proliferation of smooth muscle cells. Use of Applicants' devices and methods even for a short in vivo period with low level expression can yield valuable information for research and diagnosis of restenotic disease, as well as provides significant therapeutic effects to counter restenosis following vascular grafting and angioplasty.

As stated in a recent Lancet editorial (Vol 347: 752, 1996, copy enclosed), in which Applicants' work was reviewed along with other vascular gene therapy examples, restenosis "is ideally suited for gene therapy". This is due in part to the acute nature of the disease, from which most susceptible patients develop clinical signs in the first 3-4 months. Based on these facts, it is contemplated that "many patients with vascular

disorders might obtain substantial therapeutic benefit from gene expression that lasts only a few weeks." (id.). Thus, in one recent study reviewed in conjunction with Applicant W. Osborne's work, restenosis marked by smooth muscle cell proliferation decreased by 50% using an adenoviral vector to introduce a cytopathic gene into smooth muscle cells at the site of balloon injury. (id.)

In view of the foregoing, Applicants have provided numerous working examples of their basic devices and methods. These examples are of a diverse and detailed nature, and clearly "correlate reasonably" with the full scope of intended uses for Applicants' engrafting devices and methods. It would be and unfounded to deny protection for Applicants' engraftment devices based on the exhaustive gene therapy examples required by the Examiner. Such a denial would contravene the long established enablement review standard, calling only for a "reasonable correlation" between Applicants' disclosure and the scope of protection sought in their claims. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 706.03(n)[2].

With regard to Applicants' specific claims directed to delivery of therapeutic products to mammalian subjects, it is sufficient that Applicants' have disclosed a number of working examples reasonably correlated with the scope of these claims presented for consideration. Operable species within these claims are not required to include all possible gene therapeutic methods, or to provide a cure or therapy for all symptoms in all

---

[2] Satisfaction of the enablement requirement is not precluded even by a necessity for "considerable" experimentation to practice the invention throughout the scope of the claims, so long as such experimentation is not "undue." *In re Jackson*, 217 USPQ 804 (BPAI 1982; *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). (For explanation, see *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); holding that undue experimentation does not arise merely from a requirement to conduct syntheses and bioassays to determine operable species).

patients. On the contrary, it is sufficient that Applicants have disclosed representative examples for achieving therapeutic gene expression, demonstrated for a range of accepted model systems in vivo. Applicants have amended their claims previously, and further herein, to better clarify the claims in this regard.

Contrary to the Examiner's position, Applicants enablement requirement under 35 U.S.C. § 112 is not to resolve every aspect and contingency of a limitless "therapeutic paradigm," but to render their devices and methods useful and enabled in vivo for a reasonable range of applications commensurate with the scope of the claims. Applicants have clearly achieved, and considerably surpassed, this level of disclosure to support their claims, which teachings are thoroughly evinced by the specification and supplemental evidence submitted herein and elsewhere in the record.

Taking just one example from the foregoing discussion, Applicants have successfully expressed G-CSF according to the invention in vascular smooth muscle cells of rats[3] and provided therapeutic levels of the cytokine (as measured by, e.g., therapeutic increases in neutrophil counts) for at least seven weeks. Lejnieks et al., Human Gene Ther. (submitted for publication, previously submitted as Exhibit 4 to Applicants' April 2, 1996 Amendment). Additional data in a canine model system, offered again for the Examiner's review upon request, shows therapeutically relevant increases in neutrophil production correlated with G-CSF expression from implanted, seeded PTFE grafts. More specifically, neutrophil levels increased from control levels of 5,000-6,000 PMN/microliter to post-treatment levels of 8,000-9,000 PMN/microliter, after three months of

---

[3] The Federal Circuit in *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1898 (1996), held that the term "patient" in a patent claim is sufficiently broad to include laboratory rats used as models for in vivo testing.

treatment according to the invention (see, e.g. Osborne et al., *Clin. Res.* 41: 194A, 1993). The seeded grafts, removed after three months of in vivo activity, yielded healthy transduced cells that secreted G-CSF in culture (id.). These and other successful in vivo applications of the invention, detailed herein and elsewhere in the record, demonstrate that Applicants have taught how to make and use their invention in a manner reasonably commensurate with the scope of claims presented, such that any experimentation required to determine operable and inoperable species within the claims would be routine to the ordinarily skilled artisan.

In view of the foregoing, Applicants respectfully submit that all of the pending claims, as amended herein, completely fulfill the requirements for patentability under 35 U.S.C. § 112, first paragraph.

Patentability under 35 U.S.C. § 103

The Examiner rejected claims 1-4, 8-11, 13, and 16-20 under 35 U.S.C. § 103 as being allegedly unpatentable over Zalewski et al. (WO 93/15609) in view of Nabel et al. (U.S. 5,328,470) and Anderson et al. (WO 90/224,525).

Specifically, the Examiner cites Zalewski et al. as the primary reference supporting the rejection, which reference allegedly teaches devices for transforming smooth muscle cells to treat vascular disorders, and "the use of implant devices to hold and contain said vascular smooth muscle cells." Nabel is cited for disclosing in situ transduction of endothelial and smooth muscle cells of an arterial wall, or the deposition of cells transduced ex vivo, using a catheter to deposit cells or a gene transfer vehicle. Anderson is cited for teaching a vascular graft coated with genetically modified, autologous endothelial cells to deliver various therapeutic products, including erythropoietin, GM-CSF, Factor IX and others.

Applicants respectfully submit that the rejection under 35 U.S.C. § 103 fails to establish a prima facie case of obviousness, because the primary reference may have been misinterpreted and does not appear to disclose the subject matter which the Examiner alleges to be taught. Specifically, Zalewski et al. do not disclose any form of "implant devices to hold and contain ... vascular smooth muscle cells," nor does the primary reference disclose any comparable methods to those of Applicants' invention.

On the contrary, the devices and methods taught by Zalewski et al. are entirely inapposite to Applicants' claimed devices and methods for implanting vascular grafts seeded with autologous transduced smooth muscle cells. The Zalewski reference only teaches "injection and transcatheter delivery devices to deliver a solution" or a "perfusate" under pressure, containing only genes and vectors to transform smooth muscle cells in situ (see, e.g. page 8, lines 21-23; page 9, lines 14-35, page 10, lines 4-8). The use of these devices is transitory, i.e. lasting 1-2 minutes, based on the requirement for occlusion of the target vessel and concomitant risk of myocardial infarction (see, e.g. page 10, lines 4-8). There is absolutely no disclosure or suggestion of devices or methods "to hold and contain" transduced smooth muscle cells, particularly in the manner of Applicants' prosthetic devices which are seeded with cells and implanted as a long term graft.

Accordingly, the primary reference was improperly construed and does not support the rejection. The proposed combination to assemble Applicants' invention from the cited references, which relied on the erroneously construed primary reference, is clearly neither taught nor suggested as argued by the Examiner.

In fact, Zalewski et al. teaches away from Applicants' devices and methods by disclosing in situ transduction devices

which can only be employed as delivery vehicles for solutions and perfusates, on a transient basis. The reference expressly teaches that the transcatheter delivery devices can only be interposed within the patient's vasculature for 1-2 minutes without unacceptable risk of infarction (see, e.g. page 10, lines 4-8). In contrast, Applicants' devices and methods deliver transduced cells and physically replace or bypass existing vessels, thereby allowing safe, prolonged and highly regulatable delivery for gene therapy.

In this context, the teachings of Zalewski et al., which lead away from the long-term delivery engrafting devices and methods of the invention, are important indicia of non-obviousness, which must be considered in evaluating the patentability of the Applicant's invention. In re Braat, 16 USPQ2d 1812 (Fed. Cir. 1990). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a path divergent from that taken by the applicant." In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). "[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." Gurley, at 1131. Further, a reference teaches away "if it leaves the impression that the product would not have the property sought by the applicant." Gurley, at 1132. In this regard, the Federal Circuit has articulated a "useful general rule" that "a reference that 'teaches away' can not serve to create a prima facie case of obviousness." (id.)

Applicants previously addressed and distinguished the teachings of Nabel and Anderson in combination with the formerly cited primary reference, Noishiki et al. (US 5,387,236) (see Office Action dated October 2, 1995, Paper No. 6). Applicants recognize the Examiner's withdrawal of Noishiki et al. as a

primary reference in response to their April 2, 1996 Amendment (incorporated herein by this reference), and submit that the record thereby indicates that all of these references have been satisfactorily addressed and overcome.

In view of the above amendments to the claims and accompanying remarks, Applicants believe that each rejection has been addressed and overcome and that the application is now in condition for allowance. Early notice to that effect is earnestly solicited.

If for any reason, however, the Examiner feels that a telephone conference would expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 206/467-9600.

Respectfully submitted,

Dated: February 6, 1997 By: _____
Jeffrey J. King
Reg. No. 38,515

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Fl.
San Francisco, California 94111
(206) 467-9600